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Paraneoplastic syndromes (PNSs) describe collective noncancerous symptoms caused in reaction to a neoplasm. This can be due to a number of causes such as abnormal or abnormally enhanced production of biologically active hormones, cytokines, growth factors or tumour-induced antigen-antibody interactions. PNS has to be differentiated from tumours infiltrating the skin directly, like cutaneous lymphoma or the histiocytosis complex. Although PNSs are rare skin diseases, affecting most often older animals, their recognition is important for early diagnosis and adequate treatment of the underlying neoplasm. One of the best known PNS is hyperadrenocorticism, where bilateral symmetric alopecia, polyuria/polydipsia, polyphagia etc. mirror the cortisol-excess by an adenoma of the adrenal gland.

Metabolic Epidermal Necrolysis (MEN)

MEN is an uncommon cutaneous paraneoplastic syndrome occurring in older dogs and rarely in cats. Synonyms include superficial necrolytic dermatitis, hepatocutaneous syndrome and necrolytic migratory erythema. Aetiologically either a glucagon-secreting pancreatic neoplasm or a chronic liver disease can be detected. The pathogenesis is poorly understood, but may include a nutritional imbalance or deficiency. Plasma amino acid concentration seems to be significantly decreased in affected dogs, as shown by Outerbridge and co-workers. The main skin lesions include severe hyperkeratosis with fissures of footpads, as well as erythema, crusting, and erosions on pressure points like elbow and hocks, mucocutaneous junctions, and oral cavity. Secondary pyoderma or malassezia dermatitis are frequent. Pruritus can be minimal to intense and some lesions seem to be painful. During the cause of the disease systemic signs like inappetence, weight loss and concurrent diabetes mellitus may occur. The diagnostic workup includes skin biopsy and the localisation of the neoplasm. Histopathology reveals a typical “French flag”, which is composed of epidermal parakeratosis, inter- and intracellular oedema, and hyperplastic basal cells. Abdominal ultrasonography of the liver is also useful, as the typical Swiss cheese-like appearance is deemed pathognomonic. As assessment of the pancreas can be difficult with ultrasound, computed tomography, magnetic resonance imaging, and exploratory laparotomy can help to locate the primary tumour and

metastasis. The primary aim of the treatment is the surgical excision of the glucagonoma, which would then be curative. However, by the time of diagnosis metastasis are often already present. Even then a debulking is recommended, as it will lead to significant palliation of the symptoms. In animals with liver disease where no glucagonoma is detected, parenteral supplementation with amino acids or an oral high-protein- along with zinc-supplementation may lead to improvement of the skin lesions. Somatostatin analogues (octreotidum) have a significant improving effect in people with GS; unfortunately total resistance has been reported to occur after a mean of 2 years. So far only one case report describes its use in a dog with MEN^2. Prognosis is guarded with a mean survival time of 6.5 months.

Feminisation Syndrome (FS)

The FS occurs by 24-57% of dogs with a Sertoli cell tumour, which results in hormonal imbalance. Newest data indicate an association between hyperestrogenism and the FS. However, as not all affected dogs have elevated levels of oestradiol-17β, it has been proposed that the shift of the balance between oestradiol and testosterone may be more important than the absolute level. Clinical signs include attractiveness to other male dogs, gynecomastia, and a pendulous prepuce. Other signs may include bone marrow toxicity and squamous metaplasia of the prostate. The skin lesions are characterized by slowly progressive bilateral symmetric alopecia on the neck, lumbar region, and the perineum. Linear preputial dermatosis is common and coat colour change and macular melanosis can also be detected. The testicular tumour can often be easily palpated. Otherwise ultrasonography can be helpful diagnostic tool. Skin histopathology is unspecific. Estrogen-induced bone marrow suppression is rare but a potential life-threatening complication. The calculation of the testosterone/oestradiol ratio seems to be more reliable then the measurement of individual hormone levels in order to diagnose a FS. Therapy consists of bilateral castration and the diagnosis is confirmed by histopathologic examination of the neoplastic testicles.

Nodular Dermatofibrosis (ND)

ND is a syndrome affecting mainly middle-aged to older German shepherd dogs. It is associated with renal cystadenocarcinoma, cystadenoma and less commonly with uterine muscular tumours. It seems to be an inherited disease based on a mutation in a small chromosomal region that overlaps the human Birt-Hogg-Dube locus. An increased production of the cytokine TGF-β1 has been demonstrated, suggesting that it could be important for the induction of this syndrome. The dermatological clinical feature include multiple, firm, well-circumscribed dermal to subcutaneous

nodules. The diameter ranges from few millimetres up to 4cm. The overlying epidermis is mostly intact, but can become alopecic, hyperpigmented and in some instances even ulcerated. The nodules are nonpruritic and can be found primarily on the limbs. Histopathologically the nodules are composed of structurally normal collagen bundles. The kidneys can be evaluated by palpation, radiography, ultrasonography, computed tomography or contrast nephrography. As no curative treatment exists, the prognosis remains poor. The mean survival time after first observation of ND is about 2.5 years.

Paraneoplastic Pemphigus (PNP)

PNP is a rare autoimmune blistering skin disease associated with concurrent neoplasia. So far, only two cases of PNP have been demonstrated in dogs; a Golden retriever with splenic sarcoma and a Bouvier with thymic lypmphoma. The pathogenesis remains unclear. Dermatological symptoms consisted of severe erosions affecting mucocutaneous junctions, the oral cavity, but also the haired skin. Histopathology reveals a combination of pemphigus vulgaris and erythema multiforme. None of the dogs survived.

Erythema Multiforme Associated with Thymoma

Erythema multiforme was diagnosed in a middle-aged Labrador retriever with concurrent thymoma. His main complaints were halitosis, hyperemic buccal mucosa and gingiva along with dermatological symptoms. The skin lesions consisted of depigmentation of the nasal planum and target lesions, scaling, erosion and ulceration affecting initially the preputial and peripreputial area, as well as the pinnae. The lesions further progressed on the ventral abdomen and dorsum. Histologically an erythema multiforme was confirmed. Radiography revealed a mediastinal mass and histopathology was consistent with thymoma. 4 months after excision the skin condition was well controlled without medication. Therefore erythema multiforme may be a paraneoplastic disorder associated with thymoma in the dog.

Paraneoplastic Exfoliative Dermatitis (PED)

PED is a syndrome only reported in cats associated with a thymoma. The pathogenesis is not fully understood, but an auto-immune process is suspected. Mainly older cats are affected presenting with severe exfoliation or scaling, and erythema without pruritus. The lesions start on the head and

pinna, becoming generalised. With progression and increased severity alopecia can develop also. The dermatological lesions seem to precede the systemic signs, including non-specific anorexia, lethargy and sometimes coughing or dyspnoea. Histopathological changes are characterised by cell-poor hydropic interface dermatitis affecting the epidermis and the hair follicle, as well as apoptosis of keratinocytes, satellitosis and a lymphocytic dermal infiltrate. Radiography confirms the mediastinal mass. Ultrasound, cytology and/or true cut biopsies further confirm the thymoma (usually benign). Surgical resection is the treatment of choice and if the thymoma is excisable the prognosis is good and skin lesions improve within a few months. Metastasis is rare. Unfortunately the tumour resectability is often impossible to predict preoperatively.

Pancreatic Paraneoplastic Alopecia (PPA)

PPA is another paraneoplastic disease so far only described in middle-aged to older cats. It is reported mostly in association with pancreatic carcinoma and less often with biliary carcinoma. The pathogenesis is unclear. The most striking dermatological signs are acute, progressive symmetrical alopecia, easily epilated hairs and an underlying shiny and thin skin. Some cats groom excessively, which leads to the postulation that thereby the stratum corneum is exfoliated leading to the shiny skin. The lesions affect mainly the limbs, flanks and the face. Eventually they can become generalised. Foot pads are also effected, either presenting dry, crusted and fissured, or erythematous and moist. Secondary *Malassezia*-dermatitis is possible. Systemic signs can include weight loss, inappetence, vomiting, diarrhoea and lethargy. Histopathological evaluation reveals mainly the absence of the stratum corneum, marked follicular telogenisation, miniaturization and atrophy. Ultrasound and computed tomography are helpful tools in demonstrating the tumour and its metastases. Thoracic radiography helps to reveal pulmonary metastases. As in the vast majority of cases, the neoplasia has already metastasized, the prognosis is grave.

Selected References

1. TUREK MM: Cutaneous paraneoplastic syndromes in dogs and cats: a review of the literature. Veterinary Dermatology, 2003; 14: 279-296.
2. OUTERBRIDGE CA, MARKS AL and ROGERS QR: Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis. Veterinary Dermatology, 2002; 13: 177-186

3. OBERKIRCHNER U et al.: Successful treatment of canine necrolytic migratory erythema (superficial necrolytic dermatitis) due to metastatic glucagonoma with octreotide. Veterinary Dermatology 2010;21(5):510-6
4. SCOTT DW, MILLER WH and GRIFFIN CE: Muller & Kirk's Small Animal Dermatology. 6th Edition. W. B. Saunders Company. 2001
5. ELMORE SA et al.: Paraneoplastic pemphigus in a dog with splenic sarcoma. Veterinary Pathology, 2005; 42: 88-91
6. LEMMENS P et al.: Paraneoplastic pemphigus in a dog. Veterinary Dermatology, 1998; 9: 127-134
7. TEPPER LC et al.: Diagnosis of erythema multiforme associated with thymoma in a dog and treated with thymectomy. Journal of the American Animal Hospital Association, 2011; 47: 19-25